Amendments to the Drawings:

The attached replacement drawing sheet includes changes to Fig. 3 and replaces the original sheet that included Fig. 3. In Fig. 3, "wt V174A" has been amended to read "wt V174V."

Attachments following last page of this Amendment:

Replacement Sheet (1 page)

REMARKS

Upon entry of the above amendment, claims 1-4, 7-15, and 18-22 will be pending, claims 5-6 and 16-17 having been canceled without prejudice to continued prosecution and new claim 22 added. The claims have been amended to specify that the therapeutic agent is rosuvastatin and the cells are liver cells. Support for these amendments can be found, for example, in original claim 5 and in the specification at page 1, lines 5-7. Claim 13 is amended to specify measuring the level of OATP-C polypeptide expression; this language is supported by claim 13 as originally presented, and also by the specification at page 5, lines 1-16. Other amendments merely clarify the scope of the claims and/or omit superfluous language. Support for new claim 22 can be found, for example, at page 16, lines 24-28 of the specification. No new matter has been added.

Table 1 of the specification has been amended to clarify that the *1a and *5 alleles contain an asparagine residue (Asn) at position 130 and that the *1b, *14, and *15 alleles contain an aspartic acid residue (Asp) at position 130. Support for the amendments to Table 1 can be found, for example, at page 20, line 15, and line 32, and at page 21, line 13 of the specification. No new matter has been added.

Applicants confirm the species election of a polymorphism of an alanine at position 174 of SEQ ID NO:1. The election is made without traverse. The elected species reads on claims 1, 4, 7-12, 15, and 18-22. Claims 2-3 and 13-14 are presently withdrawn from consideration by the Examiner. Applicants understand that these claims will be examined once claims drawn to the elected species are deemed allowable.

Drawings

The Examiner objected to Figure 3 for referring to the wild-type allele as "V174A" instead of "V174V." A replacement Figure 3 is enclosed in which the wild-type allele is correctly identified. Applicants thank the Examiner for pointing out the error, and respectfully request that the objection to the drawings be withdrawn.

Specification

The Examiner objected to the specification for containing an embedded hyperlink at page 18, line 11. The specification at page 18, line 11 has been amended to delete the hyperlink. Accordingly, the Office is requested to withdraw the objection to the specification.

Claim Objections

The Examiner asserted that "should claims 5-10 be found allowable, claims 16-21 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof." Claims 16 and 17 have been canceled without prejudice. Claims 18-21 have been amended to depend from claim 11. Accordingly, amended claims 18-21 cannot be characterized as substantial duplicates of any of claims 5-10.

Rejection under 35 U.S.C. §112, first paragraph, lack of written description

The Examiner rejected claims 1, 4-10, and 16-21 under 35 U.S.C. §112, first paragraph, for an alleged lack of written description. The Examiner asserted that:

> In the current situation, the definition of the allele of a polymorphism in linkage disequilibrium with a codon encoding alanine at position 174 of SEQ ID NO:1 lack any specific structure, is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the 13 specific polymorphisms, is in the absence of knowledge of the material composition and fails to provide support for the generic claim to a polymorphism in linkage disequilibrium with a codon encoding alanine at position 174 of SEQ ID NO:1.

Claims 5-6 and 16-17 have been canceled. Amended claims 18-21 now depend from claim 11, which was not included in the rejection. Thus, the rejection is moot as to them. Applicants respectfully disagree with the rejection as applied to claims 1, 4, and 7-10.

Applicants respectfully assert that the description of 12 polymorphisms in linkage disequilibrium with a codon encoding alanine at position 174 of SEQ ID NO:1 provides sufficient written description for the genus recited in claim 1(b)(ii). Under U.S. law, description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. Furthermore,

a representative number of species is an inverse function of the skill and knowledge in the art. See, MPEP §2163.II.3a.ii. Here, techniques for determining if an allele is in linkage disequilibrium (LD) with a given polymorphism are well known. See, for example, the Jorde reference (*Genome Research*, vol. 10, pp. 1435-1444 (2000), ref. AJ on the Form-1449 submitted with the Information Disclosure Statement of January 25, 2006), which indicates that LD measurements have been commonly used since 1964. See page 1435 of Jorde. The Jorde reference also indicates that there are at least 11 different programs available for LD analysis (see Table 2). Thus, in view of the specification and knowledge in the art, one of ordinary skill would have realized that the inventors provided a representative number of species within the genus of alleles in LD with a codon encoding alanine at position 174 of SEQ ID NO:1. Accordingly, the Examiner is asked to withdraw the rejection under 35 U.S.C. §112, first paragraph, for lack of written description.

Rejection under 35 U.S.C. §112, first paragraph, lack of enablement

The Examiner rejected claims 1, 4-12, and 15-21 under 35 U.S.C. §112, first paragraph, for an alleged lack of enablement. Applicants respectfully disagree with the Examiner. However, in an effort to move the case to allowance, Applicants have canceled claims 5-6 and 16-17 without prejudice and amended claims 1, 4, 7-12, 15, and 18-21 to recite that the therapeutic agent is rosuvastatin and the cells are liver cells.

The Examiner cited to Lee *et al.* (*Clin Pharmacol Ther*, vol 78, pp. 330-341, 2005), asserting that "Lee *et al.* concluded that the heterozygotes for the 521 T>C polymorphisms did not differ significantly in the pharmacokinetic parameters of rosuvastatin as compared to the TT homozygotes in white subjects." The Examiner also asserted that the findings presented by Lee *et al.* "directly contradict the conclusions drawn by the inventors of the instant application. Applicants respectfully disagree.

The Lee *et al.* reference indicates on the last paragraph of page 336 that "[a]mong white subjects, there was a significant effect of T521>C genotype on AUC_{0-t} (P= .001). AUC_{0-t} was higher in 521 C homozygotes (CC) than in heterozygotes (TC) and in 521T homozygotes (TT)."

While a significant difference may not have been observed between TT homozygotes and TC heterozygotes in the Lee *et al.* study, CC homozygotes certainly had higher plasma levels of rosuvastatin, consistent with the teachings of the present invention. Furthermore, Figure 2 of Lee *et al.* shows a definite trend to higher plasma levels not only in CC homozygotes compared to TC heterzygotes and TT homozygotes, but also in TC heterozygotes compared to TT homozygotes. Furthermore, Lee *et al.* indicate on page 340 that "[o]ur results, of course, do not exclude the possibility that a larger sample could show an effect of heterozygosity on rosuvastatin plasma concentration." Thus, the conclusions of the Lee et al. reference are not inconsistent with the teachings of the present specification. The Office's conclusion that Lee *et al.*'s results "definitely contradict" the present inventors' conclusions is simply not true.

The Examiner also asserted that the study of Lee et al. "points to significant differences between the pharmacokinetic parameters of rosuvastatin in Asian vs. Caucasian subjects with the same allelic composition of the V174A polymorphism." While this statement is true, it is not pertinent to the question of whether the present claims satisfy the enablement requirement.

The Lee *et al.* reference indicates that Asian populations taking rosuvastatin had a higher exposure (i.e., higher plasma level of the drug) than Caucasians on the same drug dose and that this difference cannot be explained by the V174A mutation. As shown in Figure 2 of Lee *et al.*, the numbers within each ethnic group (except possibly the Asian-Indian group) showed a trend to higher drug plasma levels' corresponding to the presence of the V174A allele. (In the Asian-Indian group, there were only 5 individuals (out of 35 total) who were heterozygous for the V174A allele (and none who were homozygous), so it is difficult to draw any conclusions about the significance of the results in that group.) Therefore, Applicants submit that *within any given ethnic population*, the V174A mutation can be presumed to be associated with reduced transport of rosuvastatin, and correspondingly higher plasma levels of the drug. The fact that other genetic factors may contribute to the observed differences between Caucasians and Asians does not mean that the V174A polymorphism has no diagnostic relevance. Clearly it does.

Accordingly, no undue experimentation would be required to practice the methods of claims 1, 4, 7-12, 15, and 18-21. Applicants request that the Examiner withdraw the rejection of claims 1, 4, 7-12, 15, and 18-21 under 35 U.S.C. §112, first paragraph, for lack of enablement.

Rejection under 35 U.S.C. §102(b)

The Examiner rejected claims 1, 6, 11, 15, and 17 under 35 U.S.C. §102(a) as being anticipated by Nishizato *et al.* (*Clin. Pharmacol. Ther.*, vol. 73, pp. 554-565, 2003). The Examiner asserted that Nishizato *et al.* teach a method of diagnosis comprising the steps of claim 1, and further teach alanine at position 174 and mention pravastatin, citing the Abstract, pages 556-57, and Table 1 of Nishizato *et al.*

Claims 6 and 17 have been canceled without prejudice. Independent claims 1 and 11 have been amended to specify that the therapeutic agent that is transported is rosuvastatin. The cited reference does not teach that a polymorphism at position 174 is associated with reduced ability to transport rosuvastatin, and in fact does not even mention rosuvastatin. As such, the Nishizato et al. reference does not anticipate any of the present claims. The Examiner is requested to withdraw the rejection of claims 1, 11, and 15 under 35 U.S.C. §102(a).

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 4 and 12 under 35 U.S.C. §103(a) as being obvious over Nishizato *et al.* in view of Adeokun *et al.* (EP 1186672). The Examiner asserted that "it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have adjusted the dose of statin in subjects with the OATP-C polymorphisms of Nishizato et al., since the subjects were unable to take up all available statin due to the OATP-C transporter mutation, thereby reducing effectiveness of the treatment."

Claims 4 and 12 respectively depend from claims 1 and 11, which have been amended to specify that the therapeutic agent is rosuvastatin. The Nishizato *et al.* reference does not teach or suggest that a polymorphism at position 174 is associated with reduced transport of rosuvastatin. The Adeokun *et al.* reference does not remedy the deficiencies of the Nishizato *et al.* reference,

as Adeokun *et al.* does not indicate that a polymorphism at position 174 is associated with reduced transport of rosuvastatin. As such, the combination of cited art does not render claims 4 and 12 obvious. The Examiner is asked to withdraw the rejection of claims 4 and 12 under 35 U.S.C. §103.

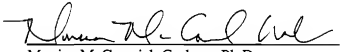
CONCLUSION

Applicants respectfully submit that claims 1, 4, 7-12, 15, and 18-22 (and also withdrawn claims 2, 3, 13, and 14) are in condition for allowance, which action is respectfully requested.

Please apply the three-month Petition for Extension of Time fee and any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 06275-0492US1.

Respectfully submitted,

Date: 11/12/08



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